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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BORGEEST, CHRISTINA M	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/519,890	FORBES, BRIONY	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *8-11,13-17,25-28 and 30-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 12, 18-24, 29 and 34-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of a first ECM binding sequence of SEQ ID NO: 10 and a second ECM binding sequence of SEQ ID NO: 16 (which Applicant states reads on claims 1-5, 18-22 and 35-41) in the reply filed on 23 June 2006 is acknowledged. The traversal is on the ground(s) that the subject matter within the claims (the sequences recited in claims 4, 5, 21, 22) is sufficiently narrow to provide the Examiner with a limited number of embodiments to search with administrative efficiency.

Applicant states that the sequences of first ECM site is suggested on the basis of homology with the consensus sequence for matrix binding proteins (line 29, 30 page 4 of the present specification) and that the second ECM binding site, the selection of the variants is the result of comparison with other similar sequences with other binding proteins, as presented in the instant specification on page 6, and that several of the mutations have been tested, with which the Examiner takes no issue.

The argument is not found persuasive because each mutation of the claimed product (polypeptide) represents a separate and non-obvious contribution to the art, in other words, Applicants have disclosed the basis of their selection of amino acid mutations, however, neither the specification nor Applicant's arguments suggest that each mutation is an obvious variant. For instance, at p. 23, Applicant states that none of the mutants listed at line 4 were resistant to proteolysis, whereas at p. 24, Applicant states the mutations listed in lines 1-2 could protect from proteolysis, thus it appears

there are differences in the performance of the mutants. In addition, Applicant states at p. 5 the invention "preferably provides for the alteration of both ECM binding sites", thus stating that the preferred embodiments are proteins comprising mutations of both ECM binding sites, thus the actual number of preferred embodiments would exceed the sequences listed in claims 4, 5, 21 and 22. However, if Applicant would like to state on the record that the amino acid mutations represented by the sequences recited in claims 4, 5, 21 and 22 are ***obvious variants***, the Examiner will vacate the species election requirement. Furthermore, the issues with examination burden are not limited to search, but rather consideration of issues such as enablement and written description.

The requirement is still deemed proper and is therefore made FINAL.

Claims 8, 9, 10, 11, 13-17, 25-28, 30-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 23 June 2006.

Claims 1, 18-20 and 35-38 are amended. Claims 40 and 41 are new. Upon reading the claims, it is the Examiner's reasoned belief that claims 7, 12, 24 and 29 also read on the claimed invention; claims 6, 23 and 34 also read on the claimed invention in part insomuch as they recite an alteration at K180A which corresponds to SEQ ID NO: 10. Thus claims 1-7, 12, 18-24, 29 and 34-41 will be examined insomuch as they read on the elected species, the alteration in the first ECM binding sequence consisting of

SEQ ID NO: 10 and the alteration in the second ECM binding sequence consisting of SEQ ID NO: 16.

Claim Objections

Claims 4, 5, 6, 21, 22, 23 and 34 are objected to because of the following informalities: The claims recite or encompass non-elected species. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3, 4, 5, 6, 7, 12, 37, 38, 39, 40 (which ultimately depend from claim 1) recite the limitation "an altered ***IGFBP*** molecule," in claims 2-7, 12, 41 and "contacting....cells with an altered ***IGFBP*** as in claim 1" in claim 37 (and claims 38 and 39 depend from 37). There is insufficient antecedent basis for this limitation in claim 1, because claim 1 recites "an altered ***IGFBP-2*** molecule." Appropriate correction is required.

Similarly, claims 19, 20, 21, 22, 23, 24, 29, 34, 35 and 41(which ultimately depend from claim 18) recite the limitation "a nucleic acid encoding an altered ***IGFBP*** molecule." There is insufficient antecedent basis for this limitation in claim 18 because

claim 18 recites "a nucleic acid encoding an altered ***IGFBP-2*** molecule." Appropriate correction is required.

Claims 1-7, 12, 18-24, 29 and 34-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant interchanges between IGFBP and IGFBP-2, throughout the claims, thus it is not clear what the metes and bounds of the claims are. Does Applicant intend to encompass all 6 known IGFBPs? Or does the claim only encompass IGFBP-2? Correction is required to obviate this rejection.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 18-21 and 35-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an altered IGFBP-2 molecule having an alteration at a second ECM binding sequence as set forth in SEQ ID NO: 16, and the polynucleotide that encodes for said IGFBP-2 molecule and methods of treatment comprising administration of said IGFBP-2 molecule, does not reasonably provide enablement for an altered IGFBP-2 molecule having an alteration first ECM binding sequence as set forth in SEQ ID NO: 10 and the polynucleotide that encodes said

IGFBP-2 molecule and methods of treatment comprising administration of said IGFBP-2 molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

First, with regard to the IGFBP-2 mutant claims (1-3), while at p. 24 of the specification, Applicant states that alterations at K180A ***and*** K181A ***could*** protect from proteolysis or inhibit interaction with the extracellular matrix, these alterations are not encompassed by SEQ ID NO: 10, which consists of the alteration also known as K180A only. The prior art is silent with respect to this particular mutant, namely, the IGFBP-2 molecule with an alteration at the first ECM binding sequence having SEQ ID NO: 10, and in the absence teaching in the prior art, Applicant should provide guidance. It is not predictable that the IGFBP-2 molecule with an alteration at the first ECM binding sequence having SEQ ID NO: 10 would be capable of inhibiting release of IGF on

contact with an extracellular matrix. Furthermore, according to the specification at p. 23, the SEQ ID NO: 10 mutant IGFBP-2 molecule is ***not*** resistant to proteolysis, making it even more unpredictable as to whether this mutant would be capable of increased binding of IGF upon contact with an extracellular matrix or exposure to a protease. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Second, with regard to the nucleic acid claims (18-21, 35-36) the claims recite a nucleic acid encoding an altered IGFBP-2 molecule able to effect

binding of IGF with high affinity upon contact with an extracellular matrix or a to a protease. However, as discussed above, only the SEQ ID NO: 16 IGFBP-2 mutant is enabled, so the nucleic acid claims are only enabled for encoding the SEQ ID NO: 16 mutant (see discussion above).

Third, with regard to the method claims (37-39), the specification discloses at p. 16, (top) and p. 22 Table 4 that the only IGFBP-2 molecules tested for ability to attenuate IGF-induced proliferation in colorectal cells seems to be a truncation protein that is not claimed and a non-elected sequence. However, Applicant discloses at pps. 20-21 (Tables 2 and 3, respectively) that the SEQ ID NO: 16 IGFBP-2 mutant (also known as K234A) appears to have reduced dissociation constants, thus provides some support for enablement of this particular IGFBP-2 molecule. The prior art is silent with respect to the reduction of proliferation comprising administration of the IGFBP-2 mutants consisting of altered ECM binding sequences (SEQ ID NOs: 10 and 16). In addition, the prior art teaches that over-expression of IGFBP-2 may be a marker for malignant transformation (Richardson et al. 2003. Virchows Arch. 442: 329-335—see abstract). In the absence of the teaching in the prior art, Applicant should provide guidance as to how to use the invention. Only in the case of the SEQ ID NO: 16 IGFBP-2 mutant in the form of reduced dissociation constants), but not the SEQ ID NO: 10 IGFBP-2 mutant, is there any support of enablement of the methods.

In addition, claims 4, 6, 23 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains

subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. (See Wands factors above).

Claims 4, 6, 23 and 34 recite the IGFBP-2 molecule with an alteration at the first ECM binding sequence having SEQ ID NO: 10, and this molecule is not enabled (see the discussion in the preceding paragraphs). Note, that in the case of claims 6, 23 and 34, that these claims were only examined to the extent that they read on the elected species, in other words, SEQ ID NO: 10.

In addition, claims 7, 12, 24, 29, 40 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. (See Wands factors above).

At p. 23 of specification, Applicant states that none of the mutants listed at line 4 (one of which is the SEQ ID NO: 16 mutant) were resistant to proteolysis, and claims 7, 12 and 40 all require that the claimed polypeptide (i.e., IGFBP-2 molecule comprising alterations in the first ECM binding sequence having the sequence of SEQ ID NO: 10 or the IGFBP-2 molecule comprising alterations in the second ECM binding sequence having the sequence of SEQ ID NO: 16) be resistant to proteolysis. In addition, claims 24, 29 and 41 are drawn to the polynucleotides encoding the claimed polypeptides, and those claims also require that the encoded polypeptides be resistant to proteolysis.

Neither the specification nor the prior art teach that the IGFBP-2 molecule comprising alterations in the first ECM binding sequence having the sequence of SEQ ID NO: 10 or the IGFBP-2 molecule comprising alterations in the second ECM binding sequence having the sequence of SEQ ID NO: 16 are resistant to proteolysis.

Due to the lack of direction/guidance presented in the specification regarding how to use the IGFBP-2 mutants having SEQ ID NO: 10 as a first ECM binding sequence; the inability of the IGFBP-2 mutants having SEQ ID NO: 10 as the first ECM binding sequence and SEQ ID NO: 16 as the second ECM binding sequence to resist proteolysis, the silence of the prior art with regard to said mutants and their ability to reduce proliferation, the absence of working examples directed to same and the complex nature of the invention, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 18, 35 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Lucic et al. (2nd citation on Applicants' 1449 form). The claims are drawn to an altered IGFBP-2 molecule able to effect binding of IGF-I OR IGF-II with high affinity

wherein an inhibited release of IGF occurs on contact with an extracellular matrix or exposure to a protease (claim 1) and the nucleic acid encoding said IGFBP-2 molecule (claim 18), and the vector having said nucleic acid (claim 35) and the host cell carrying said nucleic acid (claim 36). Lucic et al. teach a mutant of IGFBP-2 (and IGFBP-2-g3p fusion protein) and the vector for expressing the protein in the host cell (*E. coli*) see p. 96-99 (Materials and Methods) and Figure 1, p. 98). Although they do not publish the nucleic acid sequence encoding the altered IGFBP-2 molecule, it is inherent in the publication that they were in possession of such a nucleic acid sequence, as they were able to produce the altered IGFBP-2 molecule. The authors introduced a H64A subtilisin cleavage site into the fusion protein to aid in elution off the column, (see p. 103, right column, 2nd paragraph; Table 1, p. 104; p. 105, right column, 2nd paragraph) because "of the high affinity between IGF-II and IGFBP-2, mutants of IGFBP-2 with a higher affinity for IGF-II than wild-type might be difficult to elute with acid or by competition with IGF-II." The authors observed that this was even seen to some degree in the wild-type IGFBP-2. However, even with the cleavage site, enrichment levels were lower with enzymatic elution compared to elution with acid (see p. 103, right column, 2nd paragraph; Table 1, p. 104), thus the IGFBP-2 molecule taught by Lucic et al. did have inhibited release of IGF-II (when compared with acid elution methods) upon contact with a protease. Thus claims 1, 18, 35 and 36 do not teach anything new over the prior art.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 37-39 are rejected under 35 U.S.C. 102(e) as being anticipated by Yamano et al. (U.S. Patent No. 7,071,160, which has an effective filing date of 15 June 2001). The instant claims are drawn to a method of reducing IGF mediated proliferation of a population of cancerous cells, comprising administration with an altered IGFBP as in claim 1. The method claims are broader in terms of structural requirements, thus the '160 patent, which teaches at column 1, lines 58-59 that IGFBP-2 inhibits the action of IGF, and claims (columns 85-86) a medicament comprising an IGFBP molecule for the treatment of breast, prostate and colon cancer (among others). Thus claims 37-39 do not teach anything new over the prior art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest, Ph.D.

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER